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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/685,124	10/14/2003	Charles Alois Dvorak	R0067D-DIV	4517

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/685,124	DVORAK ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42, 44, 49, 53, 55-59* is/are rejected.

7)☒ Claim(s) *43,45-48,50-52 and 54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10142003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 42-59 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of detrusor instability, does not reasonably provide enablement for all other treatments embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the activity related to muscarinic M2/M3 receptor activity provided in the specification. Claim 56 recites 'pharmaceutical composition .... suitable for administration to a subject having a disease state which is alleviated by treatment with a M2/M3 muscarinic receptor antagonist' and claim 57 recites "a method of treatment comprising administering to a subject in need of such treatment..."

without reciting what type of treatment is intended (see the rejection under 35 U.S.C. 112, second paragraph below). Claims 58-59 are also very open and does not specifically set forth what diseases types are intended. If treatment of diseases in a subject are intended, then the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having muscarinic receptor antagonistic activity, useful to treat a wide list of diseases, which include smooth muscle disorders, respiratory tract disorders, etc. Test procedures and assays are provided in Examples 17-20 and it is concluded the 'the compounds of the invention were active' (see pages 90-94), however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims.

The state of the art provides the unpredictability of the muscarinic antagonistic activity related to pharmacological therapeutic interventions. Hegde et al. (Life Sciences, 1999) in their study related to muscarinic receptors in urinary bladder, concluded that 'the contractile mechanisms need further investigation' (see page 426). Eglen et al. (Trends Pharm. 1994) stated that "the lack of discriminating pharmacological tools (particularly a selective M2 receptor agonist) poses considerable difficulties in pharmacologically isolating a muscarinic receptor subtype" (see page 118). Eglen et al. (Pharmacol. Rev. 1996) regarding the functional role(s) of muscarinic receptors in smooth muscle, concluded that "The physiological consequences of this model remain unknown, although one may speculate on its function" (see page 556). Alabaster (Life Sciences 1997) regarding the use of muscarinic antagonistic agents in the treatment of airway obstructive diseases, stated that "The role of M2 receptors in these smooth muscle

preparations is unknown" (see page 1058). Osayu et al. (Arzneim. Forsch./Drug Res. 1994) in their publication on pharmacological action of antimuscarinic compounds, expressed that "further studies are needed to define the details of these mechanisms" (see page 1248). Eglen et al. (Emerging Drugs 1998) regarding the therapeutic potential of selective modulators of muscarinic receptor subtypes, emphasized that "Since relatively little is known regarding the pathophysiological changes in the proportions of muscarinic receptor subtypes expressed, the prediction of therapeutic potential of novel ligands is difficult and complex" (see page 68). Caulfield et al. (Pharm. Rev. 1998) regarding muscarinic receptor subtypes, remarked that "serious errors can be made in estimates of antagonist affinity constants by inappropriate design of radioligand binding experiments" (see page 282) and further concluded that "the paucity of highly selective antagonists, and the lack of any selective agonists has impeded the unambiguous identification of muscarinic receptor subtypes mediating many important responses" (see page 288).

As can be seen from above, the state of the art clearly establishes the unpredictability in therapeutic interventions using muscarinic antagonists. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the

unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42, 44, 49, 53, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al., CAPLUS Abstract 86:29756. The reference teaches substituted tretrahydropyrimidine compounds having filaricidal activity, see the compound RN 61322-07-4 disclosed in the enclosed copy of CAPLUS Abstract. The instant claims recite that R^4 is alkyl, e.g., methyl and the reference compounds in the analogous position are unsubstituted or

substituted by H. Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2$ group and it is well established that compounds that differ by a $-CH_2$ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Allowable Subject Matter

Claims 43, 45-48, 50-52 and 54 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The references of record do not teach or fairly suggest the compounds claimed therein.

Receipt is acknowledged of the Information Disclosure Statement filed on October 14, 2003 and a copy is enclosed herewith.

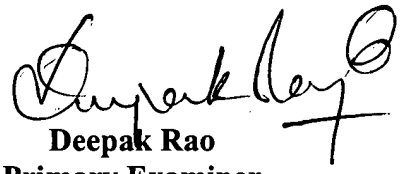
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

October 3, 2005